On February 2, 2024, FDA published the final rule to amend the Quality System (QS) regulation in 21 CFR part 820 (89 FR 7496, effective February 2, 2026). The revised 21 CFR part 820 is now titled the Quality Management System Regulation (QMSR). The QMSR harmonizes quality management system requirements by incorporating by reference the international standard specific for medical device quality management systems set by the International Organization for Standardization (ISO), ISO 13485:2016. The FDA has determined that the requirements in ISO 13485 are, when taken in totality, substantially similar to the requirements of the QS regulation, providing a similar level of assurance in a firm's quality management system and ability to consistently manufacture devices that are safe and effective and otherwise in compliance with the Federal Food, Drug, and Cosmetic Act (FD&C Act).

This guidance document was issued prior to the effective date of the final rule. FDA encourages manufacturers to review the current QMSR to ensure compliance with the relevant regulatory requirements.

On November 26, 2024, FDA issued a guidance titled "Transitional Enforcement Policy for Ethylene Oxide Sterilization Facility Changes for Class III Devices." This Ethylene Oxide Sterilization guidance provides information regarding FDA recommendations and general principles PMA and HDE holders of Class III devices sterilized by ethylene oxide (EtO) whose products are affected by the potential, actual, or temporary operation reductions at a sterilization facility may reference if they wish to have FDA consider whether the exercise of enforcement discretion relating to the implementation of certain types of sterilization site changes is appropriate.

On November 2, 2023, FDA issued a guidance titled "Enforcement Policy for Certain Supplements for Approved Premarket Approval (PMA) or Humanitarian Device Exemption (HDE) Submissions." This guidance provides clarification on FDA's policies and regulatory review expectations for certain limited modifications affecting the safety and effectiveness of a device required to have an approved PMA or the safety and probable benefit of a device required to have an approved HDE at the conclusion of the COVID-19 public health emergency.

Contains Nonbinding Recommendations

Manufacturing Site Change Supplements: Content and Submission

Guidance for Industry and Food and Drug Administration Staff

Document issued on December 17, 2018.

The draft of this document was issued on October 21, 2015.

For questions about this document regarding CDRH-regulated devices, contact the Premarket Approval Staff at 301-796-5640.

For questions about this document regarding CBER-regulated devices, contact the Office of Communication, Outreach and Development (OCOD) by calling 1-800-835-4709 or 240-402-8010.



U.S. Department of Health and Human Services
Food and Drug Administration

Center for Devices and Radiological Health

Center for Biologics Evaluation and Research

GRZAN

Preface

Public Comment

You may submit electronic comments and suggestions at any time for Agency consideration to https://www.regulations.gov. Submit written comments to the Dockets Management Staff, Food and Drug Administration, 5630 Fishers Lane, Room 1061, (HFA-305), Rockville, MD 20852. Identify all comments with the docket number FDA-2015-N-3454. Comments may not be acted upon by the Agency until the document is next revised or updated.

Additional Copies

CDRH

Additional copies are available from the Internet. You may also send an e-mail request to CDRH-Guidance@fda.hhs.gov to receive an electronic copy of the guidance. Please use the document number **1269** to identify the guidance you are requesting.

CBER

Additional copies are available from the Center for Biologics Evaluation and Research (CBER) by written request, Office of Communication, Outreach and Development (OCOD) (HFM-40), 10903 New Hampshire Ave., Bldg. 71, rm. 3128, Silver Spring, MD 20993-0002, or by calling 1-800-835-4709 or 240-402-8010, or by e-mail at ocod@fda.hhs.gov or from the Internet at http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

GRZAN

Table of Contents

I. INTRODUCTION **1**

II. BACKGROUND **1**

III. SCOPE OF GUIDANCE **3**

A. DEFINITIONS……..…3

IV. SUBMISSIONS FOR MANUFACTURING SITE CHANGES **6**

A. WHAT IS A MANUFACTURING SITE CHANGE AND WHEN SHOULD IT BE SUBMITTED AS A SITE CHANGE SUPPLEMENT VERSUS A 30-DAY NOTICE? 6
B. WHAT SHOULD BE SUBMITTED IN THE SITE CHANGE SUPPLEMENT? 11
C. DETERMINING WHETHER AN INSPECTION MAY BE NEEDED. 14
D. ADDITIONAL RESOURCES 15

GRZAN

Manufacturing Site Change Supplements: Content and Submission

Guidance for Industry and Food and Drug Administration Staff

This guidance represents the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff or Office responsible for this guidance as listed on the title page.

I. Introduction

This guidance explains FDA's current thinking regarding the following:

(A) What constitutes a manufacturing site change and when you should submit a PMA supplement for a site change;

(B) What documentation you should submit in a site change supplement; and

(C) The general factors FDA intends to consider when determining whether to conduct an establishment inspection prior to approval of a site change supplement.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidance means that something is suggested or recommended, but not required.

II. Background

Under section 515(d)(5) of the Federal Food, Drug, and Cosmetic (FD&C) Act, 21 U.S.C. § 360e(d)(5), a supplemental application to an approved PMA (PMA supplement) must be submitted for review and approval by FDA before making a change that affects the device's safety or effectiveness, unless such change is a modification in a manufacturing procedure or method of manufacture, which would be eligible for a 30-day notice. The PMA regulations provide general criteria in 21 CFR 814.39 for determining when PMA holders (hereinafter referred to as "applicants") are required to submit a PMA supplement or are eligible to submit a

30-day notice. Under 21 CFR 814.39(a)(3), a PMA holder must submit a PMA supplement when it "use[s] a different facility or establishment to manufacture, process, or package the device," and the change affects the device's safety or effectiveness.

With respect to establishment inspections, section 510(h) of the FD&C Act (21 U.S.C. § 360(h)) requires every registered establishment to be subject to inspections pursuant to section 704 of the FD&C Act (21 U.S.C. § 374) and every such establishment engaged in the manufacture, propagation, compounding, or processing of a device or devices will be inspected in accordance with a risk-based schedule.

In March 1996, CDRH sent a letter to the medical device industry that announced a one-year pilot to improve the processing of PMA supplements for changes in manufacturing sites. The letter discussed the need to improve the speed and efficiency of CDRH review and approval of manufacturing site change supplements, and stated that CDRH did not require a preapproval inspection for all manufacturing site changes. That letter described conditions under which a site generally would or would not be inspected. CDRH later developed the draft guidance entitled, "Likelihood of Facilities Inspections When Modifying Devices Subject to Premarket Approval," which was issued on August 5, 1999. This guidance was not finalized.

The PMA supplements described in the March 1996 letter and the 1999 draft guidance were called "site change supplements" or, if no preapproval inspection was required, they were termed "express supplements." FDA now identifies all such submissions as "site change supplements" with a designation of whether or not an inspection is needed before the change can be implemented. Based on feedback from industry and the Agency's experience over many years, FDA has made substantial revisions and updates to the 1999 draft guidance, which is being replaced by this guidance, "Manufacturing Site Change Supplements: Content and Submission."

This guidance is intended to help industry decide when a change in manufacturing site should be submitted in a PMA site change supplement. The guidance is also intended to help industry anticipate when a preapproval inspection in connection with a PMA supplement for a manufacturing site change will likely be needed to evaluate the firm's implementation of the Quality System (QS) regulation requirements, 21 CFR Part 820. As a result, this guidance should help firms manage the timeframes associated with implementing the changes in the manufacturing site and any processes, methods, procedures, qualifications, and validations. Regardless of whether or not an FDA preapproval inspection will be conducted, or whether a PMA supplement should be submitted, manufacturers of class III finished devices must comply with the QS regulation requirements applicable to its operations, which are found in 21 CFR Part 820. By developing and implementing QS processes, manufacturing-related problems can be minimized when using a different facility or establishment to manufacture, process, or package a device.

FDA also has issued other general guidances regarding PMA supplements and 30-day notices. In the guidance, Modifications to Devices Subject to Premarket Approval (PMA) - The PMA Supplement Decision-Making Process – Guidance for Industry and FDA Staff[1] , FDA discusses,

[1] For further information on PMA supplement decision-making process, please refer to this guidance, available at http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM089360.pdf.

in Section G, "When to Submit a Manufacturing Site Change Supplement," that it plans to issue a separate guidance on manufacturing site change supplements and when an inspection is likely to occur. This "Manufacturing Site Change Supplements: Content and Submission" guidance is that separate guidance.

FDA issued the guidance, "30-Day Notices, 135-Day Premarket Approval (PMA) Supplements and 75-Day Humanitarian Device Exemption (HDE) Supplements for Manufacturing Method or Process Changes- Guidance for Industry and FDA Staff",[2] regarding "changes FDA believes may qualify for a 30-day notice and the changes that generally do not qualify." The guidance includes an illustrative list of manufacturing procedure changes or changes to the methods of manufacture, that when they affect the safety and effectiveness of the device, would likely qualify for a 30-day notice, such as "a change that adds a new cleanroom to existing manufacturing space." The list also includes that a 30-day notice may be appropriate for a relocation of a formulation room within a manufacturing facility. The guidance explains that "existing manufacturing space can include newly constructed space or buildings provided that they are included under a single Firm Establishment Identifier (FEI). The guidance further includes examples of changes FDA believes do not qualify for submission as a 30-day notice, such as "a change in …manufacturing/sterilization site of a finished device."

III. Scope

This guidance document describes the decision-making steps that we recommend you follow to determine whether a PMA supplement should be submitted when you intend to change the manufacturing site (including a change to the processing, packaging, or sterilization site) of your legally marketed PMA-approved device. This guidance also discusses general factors FDA intends to consider to determine whether a preapproval inspection is necessary before approval of the PMA supplement.

This guidance document describes situations where a change in manufacturing site should be submitted in a PMA manufacturing site change supplement. For guidance on what changes are appropriate for reporting through other types of PMA submissions , please see the specific guidance documents listed in Section VI, "Resources."

Please note that this guidance only applies to a manufacturer of a device with an approved PMA, a product development protocol, or a humanitarian device exemption (HDE). This guidance does not address manufacturing site changes for devices cleared under premarket notification (510(k)) submissions, granted premarket authorization through the De Novo pathway, or approved and distributed as part of an investigational device exemption (IDE).

This guidance uses the term "site" to encompass both establishments and facilities. "Establishment" and "facility" are not defined in 21 CFR Part 814. For purposes of this

[2] For futher information on 30-day notices, 135-day PMA supplements, and 75-day HDE supplements for manufacturing or process changes, please refer to this guidance, available at https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM080194.pdf

guidance, FDA is using the term "establishment" as defined in 21 CFR 807.3(c), which means a place of business under one management at one general physical location at which a device is manufactured, assembled, or otherwise processed. FDA is defining the term "facility" for purposes of this guidance to mean the physical structures or buildings within an "establishment."

IV. Definitions

Unless otherwise specified, the terms below are defined as follows for purposes of this guidance only.

- **Components**: A medical device component is any raw material, substance, piece, part, software, firmware, labeling, or assembly which is intended to be included as part of the finished, packaged, and labeled device. (21 CFR 820.3(c)) A medical device component is considered an incomplete part of the finished medical device. Additionally, a component is not separately distributed (i.e., not sold or available separately) to consumers/end users, and is only sold to the manufacturer to be incorporated into the finished medical device.

- **Establishment:** A place of business under one management at one general physical location at which a device is manufactured, assembled, or otherwise processed (21 CFR 807.3(c)).

- **Facility**: The physical structures or buildings within an establishment.

- **FDA Establishment Identifier (FEI):**[3] Number used by FDA in the identification of registered establishments. A unique FEI is typically assigned to each business or entity that performs activities subject to FDA jurisdiction. Since the year 2000, FEIs have been issued with 10 digits.

- **Finished Device**: Any device or accessory to any device that is suitable for use or capable of functioning, whether or not it is packaged, labeled, or sterilized (21 CFR 820.3(l)). Additional information on accessories can be found in the guidance, "Medical Device Accessories - Describing Acessories and Classification Pathways[4]."

- **Manufacturing Site**: A facility or establishment used to manufacture, process, or package a finished device including an accessory of any finished device.

- **No Action Indicated (NAI):** Indicates no Quality System deficiencies, or Quality System deficiencies of a quantity or type to conclude that there is a minimal probability, in light of the relationship between quality system deficiencies observed and the particular device and manufacturing process involved, that the establishment will produce nonconforming or defective finished devices; this term is generally synonymous with a Situation II inspection, in which FDA informs the establishment of any objectionable findings, but generally does not initiate administrative or regulatory action. Situation II

[3] For more information on how FDA assigns FEI numbers, please refer to the agency's Field Management Directives at http://www.fda.gov/ICECI/Inspections/FieldManagementDirectives/.
[4] https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-meddev-gen/documents/document/ucm429672.pdf

inspection is defined in Part V of FDA's Compliance Program 7382.845, "Inspection of Medical Device Manufacturers[5]."

- **Official Action Indicated (OAI)**: Indicates one or more major deficiencies with the Quality System regulation such that FDA is prepared to initiate administrative and/or regulatory action, including, but not limited to, issuance of a warning letter, injunction, detention, seizure, civil money penalty, or prosecution; this term is synonymous with the definition of a Situation I inspection. Situation I inspection is defined in Part V of FDA's Compliance Program 7382.845, "Inspection of Medical Device Manufacturers[6]."

- **PMA Supplement (21 CFR 814.39(a)):** After FDA's approval of a PMA, an applicant shall submit a PMA supplement for review and approval by FDA before making a change affecting the safety or effectiveness of the device for which the applicant has an approved PMA. The only exception to this requirement is if the change is a modification to the manufacturing procedure or method of manufacture that affects safety or effectiveness that does not require submission of a PMA supplement and is eligible for a 30-day notice. While the burden for determining whether a supplement is required is primarily on the PMA holder, changes for which an applicant shall submit a PMA supplement include, but are not limited to, the following types of changes if they affect the safety or effectiveness of the device:
  (1) New indications for use of the device.
  (2) Labeling changes.
  (3) The use of a different facility or establishment to manufacture, process, or package the device.
  (4) Changes in sterilization procedures.
  (5) Changes in packaging.
  (6) Changes in the performance or design specifications, circuits, components, ingredients, principle of operation, or physical layout of the device.
  (7) Extension of the expiration date of the device based on data obtained under a new or revised stability or sterility testing protocol that has not been approved by FDA.

- **Site Change Supplement**: A PMA supplement that relates to the use of a different facility or establishment to manufacture, process, or package the device. There is no user fee required for a site change supplement; for more information regarding user fees refer to the guidance "User Fees and Refunds for Premarket Approval Applications and Device Biologics License Applications"[7].

- **Voluntary Action Indicated (VAI):** Indicates Quality System deficiencies of a quantity or type to conclude that there is a minimal probability, in light of the relationship between quality system deficiencies observed and the particular device and manufacturing process involved, that the establishment will produce nonconforming or defective finished

[5] The Compliance Program Guidance Manual for Program 7382.845 can be found at: https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM244277.pdf
[6] *See* supra n. 6.
[7] https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM345633.pdf

devices; generally synonymous with a Situation II inspection, in which FDA informs the establishment of any objectionable findings, but generally does not initiate administrative or regulatory action.

- **30 Day Notice:** A submission to FDA for changes deemed to be a modification in a manufacturing procedure or method of manufacturing of a PMA approved device. (Section 515(d)(5)(A) of FD&C Act; 21 CFR 814.39(f)).

V. Submissions for Manufacturing Site Changes

A. What is a manufacturing site change and when should it be submitted as a site change supplement versus a 30-Day Notice?

FDA has received questions on a variety of scenarios that might constitute using a different site to manufacture, process, or package a device under 21 CFR 814.39(a)(3). A typical scenario involves moving the site in which manufacturing activities take place. Other scenarios involve expanding an existing site, building a new facility or establishment, or moving equipment within a facility. Table 1 in this guidance is intended to address various manufacturing site changes that may fall under these scenarios. The table describes when a particular scenario would be considered "use [of] a different facility or establishment" for which a manufacturer should file a PMA site change supplement or when a scenario would be considered a "modification to manufacturing procedures or methods of manufacture" that is eligible for a 30-day notice.

For purposes of this guidance, FDA intends to consider a different site for which a site change supplement should be submitted to include: 1) where the site was not approved as part of the original PMA or a PMA supplement; or 2) where the site(s) was approved as part of the original PMA or PMA supplement, but only for the performance of different manufacturing activities. Under these circumstances, the different site would have no experience with either the process or the technology, or a similar process or technology, for manufacturing the same or a similar device, and FDA would not have had the opportunity to evaluate the change because it would not have been evaluated in any way in the PMA application. In such instances, we would consider the change to constitute "the use of a different facility or establishment" under 21 CFR 814.39(a)(3) and the manufacturer should submit a 180-day PMA supplement if the change affects the device's safety or effectiveness (section 515(d)(5)(A)(i) of FD&C Act). FDA recognizes that a manufacturing site change would rarely involve a completely new manufacturing technology for which the firm has no experience or the manufacture of a dissimilar device at the new site, but for completeness of defining the underlying principle for what constitutes a different site, it is important for FDA to consider both the site's familiarity with the manufacturing technology and the similarity to the devices manufactured at the site.

An applicant should submit a 180-day PMA supplement for using a different site, as described above, that affects the device's safety or effectiveness, which is also referred to as a site change supplement that FDA reviews within 180 days of receipt. See 21 CFR 814.39(a)(3), 814.39(c), and 814.40. Similarly, HDE holders are required to submit a 75-day supplement, per 21 CFR 814.108 and 814.114. The site change supplement should clearly identify any manufacturing location changes and any associated changes to the manufacturing resulting from the site change

(e.g., new facility requires changes to the water filtration for manufacturing). Manufacturing process changes that are not directly associated with the facility move should be submitted separately (e.g., 30-Day Notice or PMA Annual Report per existing regulations and guidance) and are not considered part of the manufacturing site change supplement. Refer to subsection B for additional information on what should be submitted in a site change supplement. Approval of the 180-Day PMA Supplement is needed before any manufacturing site change and related changes can be implemented.

Certain changes in manufacturing sites may be submitted as 30-day notices if they are among the sites already approved in the PMA, and if they are for performance of the same or similar manufacturing activities and for the same or similar device as those at the PMA approved site. If the previously approved site and its personnel use and have experience with similar technology and processes for manufacturing a similar device, then the new manufacturing site would not be considered "different" under 21 CFR 814.39(a)(3). Such a change would be considered a "modification" to an existing manufacturing procedure or method of manufacturing, under 21 CFR 814.39(f), and the applicant would be eligible to submit a 30-day notice if the manufacturing site change affects the device's safety or effectiveness.

FDA does not consider the use of a new facility or establishment for the manufacture, processing, or packaging of a component of a finished device to require a PMA supplement.[8] Firms that manufacture components that do not also manufacture finished devices are not subject to the QS regulation requirements, under 21 CFR 820.1(a), but these manufacturers are encouraged to use appropriate provisions of 21 CFR Part 820 as guidance. The finished device manufacturer ensures compliance with QS requirements through the application of purchasing controls (21 CFR 820.50) and acceptance criteria (21 CFR 820.80) for all components purchased or otherwise received. Thus, an applicant should submit a 30-day notice, under 21 CFR 814.39(f), for use of a new supplier of those components that are critical to the finished device's function, operation, or specifications, because such modifications to the manufacturing procedures or methods affect the finished device's safety or effectiveness. Manufacturing changes to components that are not critical to the device's function, operation or specifications do not require firms to submit a site change supplement or a 30-day notice; however,these changes must be reported in the Annual Report.[9]

Table 1 outlines the type of manufacturing site changes that FDA believes affect the device's safety or effectiveness as well as the type of submission that should be submitted to FDA. Manufacturers are responsible for validating changes, as necessary, in accordance with the QS regulations, whether or not a PMA supplement is submitted.

Table 1

[8] Please note the definition of finished devices includes accessories.
[9] *See* 21 CFR 814.39(b) and 814.84(b)(1).

Type of Manufacturing Site Change that Affects Device Safety or Effectiveness	Site Change Supplement	30-Day Notice[10]
1. Moving manufacturing, processing, or packaging activities for a finished device from one site to a new manufacturing site, both of which were approved as part of the PMA application or a PMA supplement for the subject device:		
a. If the moved activities are already conducted at the new manufacturing site.		✓
b. If the moved activities are not already conducted at the new manufacturing site	✓	
2. Moving manufacturing, processing, or packaging activities for a finished device to a new manufacturing site that was not part of the PMA application or a PMA supplement for the subject device.	✓	
3. Moving manufacturing, processing, or packaging activities for a finished device from a contract manufacturer included in the PMA application or a PMA supplement to an in-house facility previously approved in the PMA application or a PMA supplement:		
a. For activities already conducted in-house for the finished device.		✓
b. For activities not already conducted in-house for the finished device.	✓	
4. Moving manufacturing, processing, or packaging activities for a finished device from one facility to another within the same establishment that has the same FEI		✓
5. Moving manufacturing, processing, or packaging activities for a finished device into a building nearby (e.g., an office park), and the new building has a different FEI	✓	
6. Moving the manufacturing, processing, or packaging activities for a finished device to a contract manufacturer not approved as part of the PMA or a PMA supplement.	✓	

[10] For further information on 30-day notices, 135-day PMA supplements, and 75-day HDE supplements for manufacturing method or process changes, please refer to this guidance, available at https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM080194.pdf

Type of Manufacturing Site Change that Affects Device Safety or Effectiveness	Site Change Supplement	30-Day Notice[10]
7. Moving the manufacturing or processing of a *component* that is critical to the finished device's function, operation, or specification		✓

Illustrative examples are provided below that correspond with each situation identified in Table 1.

1. Moving manufacturing, processing, or packaging activities for a finished device from one site to a new manufacturing site both of which were approved as part of the PMA application or a PMA supplement for the subject device**:**

    a. If the moved activities are already conducted at the new manufacturing site for the device:

        For example, ABC, an applicant, has two sites approved in the original PMA. Both sites manufacture cardiovascular catheters. ABC plans to move and consolidate both cardiovascular catheter manufacturing lines to one of the two approved sites, which could affect the safety or effectiveness of the device. A 30-day notice should be submitted.

    b. If the moved activities are not already conducted at the new manufacturing site:

        For example, ABC, an applicant, received approval of a PMA application that included manufacturing cardiovascular catheters at the firm's Any Town, NY site and sterilizing them at the firm's Somewhere, CA site. ABC now plans to move the sterilization process into the Any Town, NY facility that manufactures the catheters. However, this Any Town, NY facility has no previous experience with this sterilization process for this device, and this move could affect the device's safety or effectiveness. A site change supplement should be submitted.

2. Moving manufacturing, processing, or packaging activities for a finished device to a site that was not part of the PMA application or a PMA supplement for the subject device:

    For example, DEF, an applicant, received approval to manufacture a spinal disc replacement device at its site in Hometown, NY. DEF now plans to manufacture the device at another site in Anywhere, CA. The Anywhere, CA, site was not included in the PMA application for the subject device. A site change supplement should be submitted.

3. Moving manufacturing, processing, or packaging activities in-house for a finished device from a contract manufacturer included in the PMA application or a PMA supplement to a facility previously approved in the PMA application or a PMA supplement for the subject device:

a. In-house from a contract manufacturer included as part of the PMA application or PMA supplement for activities already conducted in-house for the finished device:

For example, DEF, the applicant, uses contract manufacturer ABC to perform sterilization activities for DEF's cardiac stent system which is manufactured at DEF's Hometown, NY facility. DEF also performs sterilization activities in-house at the Hometown, NY facility for a previous version of the cardiac stent system which was approved in the same PMA application. DEF plans on terminating the contract with ABC and conducting sterilization activities in-house at the Hometown, NY facility for the cardiac stent system. A 30-day notice should be submitted for this change.

b. In-house from a contract manufacturer included as part of the PMA application or PMA supplement for activities not already conducted in-house for the finished device:

For example, XYZ, an applicant, uses contract manufacturer ABC to perform some of the manufacturing steps for XYZ's hip implant. XYZ plans on moving these manufacturing steps in-house. This change will require company XYZ to perform one or more manufacturing steps that it does not currently perform in-house for the PMA device. A site change supplement should be submitted.

4. Moving manufacturing, processing, or packaging activities for a finished device from one facility to another within the same establishment (same FEI):

For example, ABC, an applicant, currently performs a manufacturing step in a controlled environment (Class 100 clean room) in Building A. ABC plans to move that manufacturing step and the clean room from Building A to Building B within the same currently-approved establishment (i.e., same FEI number). A 30-day notice should be submitted.

5. Moving manufacturing, processing, or packaging activities for a finished device into a building nearby (e.g., an office park), and the new building has a different FEI:

For example, ABC, an applicant, manufactures a breast cancer companion diagnostic kit. ABC plans to move the manufacturing of the breast cancer kit to a new building. The new building will be at a different location and have a different FEI number. A site change supplement should be submitted.

6. Moving the manufacturing, processing, or packaging activities for a finished device to a contract manufacturer not approved as part of the PMA application or a PMA supplement for the subject device:

For example ABC, an applicant, manufactures an extended wear contact lens. The PMA was approved for ABC to ship the raw material buttons to a contract manufacturer for finishing and packaging. The manufacturing of the extended wear contact lens is performed by the contract manufacturer XYZ, Inc. ABC plans to move the manufacturing of the extended wear contact lens to another contract manufacturer that was not part of the PMA application or a PMA supplement. A site change supplement should be submitted.

7. Moving the manufacturing or processing of a component that is critical to the finished device's function, operation, or specification:

   For example, ABC, an applicant, currently manufactures the filter component for a slide preparation device. ABC plans to move the manufacturing of these filters to another company, XYZ. XYZ was not part of ABC's original PMA approval for the device. A 30-day notice should be submitted because that component is considered critical and the modification affects the device's safety or effectiveness. Note that this example would have the same outcome if the component manufacturing was being moved to one supplier from another, or if the component manufacturing was being moved in-house from a supplier.

   For example, ABC, an applicant, uses contract manufacturer DEF to manufacture the crystal oscillator, which is a component of ABC's implantable defibrillator. Now ABC would like to add a new company, GHI, as a second supply source for the crystal oscillator. A 30-day notice should be submitted because that component is considered critical and the modification affects the device's safety or effectiveness.

B. What should be submitted in the site change supplement?

Under 21 CFR 814.39(c), the PMA supplement must contain information needed to support the use of a different facility or establishment to manufacture, process, or package the device. In order to approve a site change supplement, the information submitted must show that, for the different site, the methods used in, and the facilities or controls used for, the manufacture, processing, and when relevant, packing and installation of the device conform to the requirements of the QS regulation, 21 CFR Part 820. See sections 515(c)(1)(C), 515(d)(2)(C) and 520(f) of the FD&C Act, 21 U.S.C. §§ 360e(c)(1)(C), 360e(d)(2)(C) and 360j(f). FDA recommends that the following information be included in a site change supplement, if applicable:[11]

1. A description of the device, intended use, and nature and purpose of the site change, including a description of the manufacturing functions that will be performed at the proposed site (e.g., assembly or incoming acceptance).

2. A diagram of the proposed new manufacturing, processing, packaging, or distribution site(s).

3. A flow diagram that identifies the steps involved in the manufacture, processing, packaging, or distribution of the device under review at the proposed site(s).

[11] For further information on manufacturing changes that may qualify for a 30-day notice please refer to FDA's final guidance, 30-Day Notices, 135-Day Premarket Approval (PMA) Supplements and 75-Day Humanitarian Device Exemption (HDE) Supplements for Manufacturing Method or Process Changes https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM080194.pdf

4. A description of the equipment and processes that would be affected by the site change.

5. A list of any standards used in the new manufacturing processes, if applicable.

6. The process validation or revalidation master plan for the site, if appropriate (including validation of software that is used as part of the production or quality system where applicable, see 21 CFR 820.70(i)).

7. A list of processes at the new site that you do not plan to validate but will verify by inspection and test.

8. The process validation or revalidation procedures (and reports, if applicable):

    a. For site change supplements for which it would be likely that FDA would conduct a preapproval inspection based on the information outlined in Section C below, we recommend that you provide the process validation or revalidation protocols for the processes requiring validation. If a determination has been made that only a subset of the process validation activities needs to be completed, then the rationale and supporting data for that decision should be supplied. For additional information on process validation, please see "Quality Management Systems – Process Validation Guidance[12]." When available, you should provide a copy of any completed validation reports[13]. All validation activities should be completed before the scheduling of an inspection. Accordingly, you should provide a date when your validation activities will be complete and you will be ready for inspection.

    b. If FDA decides not to conduct a preapproval inspection based on the information outlined in Section C below, we will likely recommend the applicant to provide the process validation or revalidation protocols and completed reports for all the processes that require validation.

9. The procedures for environmental and contamination controls, if such conditions could adversely affect the device (21 CFR 820.70). If this involves a large number of procedures, a sample of the most relevant procedures would be sufficient.

10. If different from the original PMA, any procedures that explain how inspection, measuring, and test equipment are routinely calibrated, inspected, checked, and maintained (21 CFR 820.72). If this involves a large number of procedures, a sample of the most relevant procedures would be sufficient. If procedures are the same as those

[12] Previously posted by the Global Harmonization Task Force (GHTF), this process validation guidance is now posted on the International Medical Devices Regulators Forum (IMDRF) website at http://www.imdrf.org/docs/ghtf/final/sg3/technical-docs/ghtf-sg3-n99-10-2004-qms-process-guidance-04010.pdf.

[13] See Quality System Information for Certain Premarket Application Reviews; Guidance for Industry and FDA Staff (https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm070899.pdf) for more information regarding documentation of process validation activities.

contained and approved in the original PMA, you should provide a statement indicating this.

11. If the manufacturing site change results in the use of a different supplier or contract manufacturer:

    a. Provide or reference the current purchasing control procedures detailing the supplier evaluation process and describe how you will determine the type and extent of control that is to be exercised over the suppliers. The procedures should address:

        (1) The quality controls that are established for the supplier, how those quality controls are evaluated, and how the quality controls are monitored.

        (2) The communication method for ensuring that you and the supplier fully understand all of the controls that are applicable to the supplier.

        (3) The change control mechanism utilized for ensuring adequate control over design and process related changes made by both you and the supplier.

        (4) How you maintain records of acceptable suppliers and how you address the purchasing data approval process.

        (5) How you balance purchasing assessment and receiving acceptance to ensure that products conform to specified requirements.

    b. Provide the specific documentation for any supplier, vendor, or contract manufacturer that establishes how you applied the purchasing controls (21 CFR 820.50) and acceptance activities requirements (21 CFR 820.80) to ensure the specific products and services purchased or received conform to specified requirements.[14]

12. The procedures for the incoming acceptance activities at the subject manufacturing site, if different from the procedures contained and approved in the original PMA. If procedures are the same as those contained and approved in the original PMA, you should provide a statement indicating this.

13. The procedures for the final acceptance activities at the subject manufacturing site, if applicable and different from the procedures contained and approved in the original PMA. If procedures are the same as those contained and approved in the original PMA, you should provide a statement indicating this.

[14] See comments 99, 106, and 109 in the preamble to the Quality System Regulation (61 FR 52602) for additional guidance on (1) balancing purchasing controls and acceptance and receiving activities, (2) balancing supplier and manufacturer quality controls and assurance measures, and (3) the term "quality requirements." http://frwebgate.access.gpo.gov/cgi-bin/getpage.cgi?position=all&page=52624&dbname=1996_register

C. Determining whether an inspection may be needed.

As with a premarket approval application, a supplemental premarket approval application may be approved if it meets the applicable statutory and regulatory requirements. One such requirement is that the methods used in, or the facilities or controls used for, the manufacture, processing, packaging, storage or installation of a device conforms to the requirements of section 520(f) of the FD&C Act. A preapproval inspection for a site change supplement may be necessary for FDA to find that the methods used in, or the facilities or controls used for, the manufacture, processing, packaging, storage or installation of the device conform to the requirements of the QS regulation, 21 CFR Part 820. See sections 515(c)(1)(C), 515(d)(2)(C) and 520(f) of the FD&C Act, 21 U.S.C. §§ 360e(c)(1)(C), 360e(d)(2)(C) and 360j(f).

CDRH and CBER generally determines whether to conduct an inspection of a new site associated with a site change supplement based upon the following factors:

- the dates of the last inspections of the current site and the new site;
- the classifications of the last inspections of the current site and the new site;
- the relevance of the last QS regulation inspection to the moved manufacturing, processing, or packaging activities (e.g., whether similar products or processes were inspected);
- a review of relevant recalls and adverse events, associated with manufacturing processes for devices manufactured, processed or packaged at this site; and
- the risk to the safety or effectiveness of the device associated with the manufacturing activities performed at the new site.

CDRH and CBER review the inspectional record to determine the classification of previous inspections. Inspections can be classified as Official Action Indicated (OAI), Voluntary Action Indicated (VAI), or No Action Indicated (NAI). OAI is synonymous with the definition of a Situation I inspection as defined in Part V of FDA's Compliance Program 7382.845, "Inspection of Medical Device Manufacturers."[15] Situation I indicates one or more major deficiencies with the Quality System regulation such that FDA is prepared to initiate administrative and/or regulatory action, including, but not limited to, issuance of a warning letter, injunction, detention, seizure, civil money penalty, or prosecution. NAI and VAI classifications are generally synonymous with a Situation II inspection, which indicates Quality System deficiencies of a quantity or type to conclude that there is a minimal probability, in light of the relationship between quality system deficiencies observed and the particular device and manufacturing process involved, that the establishment will produce nonconforming or defective finished devices. In Situation II, FDA informs the establishment of any objectionable findings, but generally does not initiate administrative or regulatory action.

CDRH and CBER intend to consider the factors outlined above in determining the need for an inspection at the time of review. For example, when the new site has not been inspected or the last inspection of either the current or the new site was classified as OAI, then FDA intends to

[15] *See supra* n. 6.

conduct an inspection of the new site if CDRH or CBER reviews the site change supplement and concludes that it is approvable pending a non-violative (Situation II) inspection. Manufacturers may contact the appropriate office to discuss whether a pre-approval inspection may be required; the pre-submission process may be utilized for these interactions, if appropriate.[16]

VI. Resources

The following are resources that may be of assistance in developing the content of your site change supplement or 30-day notice, preparing for an inspection, or in performing process validation:

1. Quality System Information for Certain Premarket Application Reviews; Guidance for Industry and FDA Staff, available at https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-meddev-gen/documents/document/ucm070899.pdf https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM070899

2. Guidance for Industry and FDA Staff; The Review and Inspection of Premarket Approval Application Manufacturing Information and Operations, available at https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-meddev-gen/documents/document/ucm077795.pdf

3. Guidance for Industry; Process Validation: General Principles and Practices, available at http://www.fda.gov/downloads/Drugs/.../Guidances/UCM070336.pdf.

4. Medical Devices; Current Good Manufacturing Practice (CGMP) Final Rule; Quality System Regulation, 61 FR 52602, October 7, 1996, available at http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/PostmarketRequirements/QualitySystemsRegulations/ucm230127.htm.

5. Guidance for Industry and FDA Staff: 30-Day Notices, 135-Day Premarket Approval (PMA) Supplements, and 75-Day Humanitarian Device Exemption (HDE) Supplements for Manufacturing Method or Process Changes, available at https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM080194.pdf

6. OEI (Official Establishment Inventory) Development and Maintenance Procedures, available at http://www.fda.gov/ICECI/Inspections/FieldManagementDirectives/ucm096034.htm.

7. Compliance Program Guidance Manual, Inspection of Medical Device Manufacturers. Program 7382.845, available at

[16] For more information on requests for feedback on medical device submissions, please refer to FDA's final guidance, Requests for Feedback on Medical Device Submissions: The Pre-Submission Program and Meetings with Food and Drug Administration Staff, available at https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-meddev-gen/documents/document/ucm311176.pdf

http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM244277.pdf.

8. Guidance for Industry and FDA Staff: Modifications to Devices Subject to Premarket Approval (PMA) - The PMA Supplement Decision-Making Process (2008), available at https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-meddev-gen/documents/document/ucm270606.pdf

9. Annual Reports for Approved Premarket Approval Applications (PMA) – Guidance for Industry and Food and Drug Administration Staff, available at https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-meddev-gen/documents/document/ucm089398.pdf

10. User Fees and Refunds for Premarket Approval Applications and Device Biologics License Applications, available at https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-meddev-gen/documents/document/ucm345633.pdf